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Prenatal Cotinine Levels and ADHD Among Offspring

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abstract

OBJECTIVES: An association between maternal smoking during pregnancy and offspring attention-deficit/hyperactivity disorder (ADHD) has been shown across several studies based on self-reports. No previous studies have investigated the association of nicotine exposure measured by cotinine levels during pregnancy and offspring ADHD.

METHODS: In this population-based study, 1079 patients born between 1998 and 1999 and diagnosed with ADHD according to the International Classification of Diseases and 1079 matched controls were identified from Finnish nationwide registers. Maternal cotinine levels were measured by using quantitative immunoassays from maternal serum specimens collected during the first and second trimesters of pregnancy and archived in the national biobank.

RESULTS: There was a significant association between increasing log-transformed maternal cotinine levels and offspring ADHD. The odds ratio was 1.09 (95% confidence interval [CI] 1.06–1.12) when adjusting for maternal socioeconomic status, maternal age, maternal psychopathology, paternal age, paternal psychopathology, and child birth weight for gestational age. In the categorical analyses with cotinine levels in 3 groups, heavy nicotine exposure (cotinine level. 50 ng/mL) was associated with offspring ADHD, with an odds ratio of 2.21 (95% CI 1.63–2.99) in the adjusted analyses. Analyses by deciles of cotinine levels revealed that the adjusted odds for offspring ADHD in the highest decile was 3.34 (95% CI 2.02–5.52).

CONCLUSIONS: The study reveals an association with and a dose-response relationship between nicotine exposure during pregnancy and offspring ADHD. Future studies incorporating maternal smoking and environmental, genetic, and epigenetic factors are warranted.

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Dr Sourander conceptualized the study, participated in the study design, drafted the initial manuscript, and contributed to the interpretation of the data and the critical review and revision of the manuscript; Dr Sucksdorff participated in the study design, conducted the literature search, drafted portions of the initial manuscript, and contributed to the interpretation of the data and the critical review and revision of the manuscript; Dr Chudal participated in the study design, drafted portions of the initial manuscript, and contributed to the interpretation of the data and the critical review and revision of the manuscript; Drs Surcell, Gyllenberg, Cheslack-Postava, and Brown conceptualized the study, participated in the study design, and contributed to the interpretation of the data and the critical review and revision of the manuscript; Ms Hinkka-Yli-Salomäki designed the study, conducted the analyses, and contributed to the interpretation of the data and the critical review and revision of the manuscript; and all authors approved the final manuscript as submitted.

WHAT'S KNOWN ON THIS SUBJECT: Exposure to maternal smoking is associated with various adverse perinatal outcomes. Association between maternal smoking and offspring attention-deficit/hyperactivity disorder has been shown across studies. However, the causality of the association has been questioned to be mostly due to familial confounding.

WHAT THIS STUDY ADDS: This first nationwide study, objectively measured nicotine exposure through maternal cotinine levels allows us to overcome underreporting of smoking during pregnancy. We report a strong association as well as a dose-dependent relationship between prenatal nicotine exposure and offspring attention-deficit/hyperactivity disorder.

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that quitting smoking was associated with less externalizing problems among offspring.[38] Furthermore, an American sibling study revealed that familial confounding explained inattentive but not hyperactive and/or impulsive ADHD behaviors, suggesting that the association may vary by phenotype.[39]

Despite several strengths, sibling comparison studies should also be interpreted with caution given their limitations. It has been suggested that within-sibling estimates will be biased toward the null by measurement error and that they may be either more or less biased than between-family estimates depending on the extent to which siblings share confounders versus the exposure.[40] In addition, mothers who vary in their smoking habits during different pregnancies can perhaps not be generalized to all smoking populations.[40]

It is possible that the association between nicotine exposure during pregnancy and ADHD might partially be explained also by gene-environment interaction. Accumulating data provide evidence that prenatal smoking may act through epigenetic changes via altered DNA methylation and microRNA expression.[41,42] The exposure to nicotine may increase the risk of ADHD particularly among children with genetic vulnerability for ADHD. It is also possible that maternal smoking during pregnancy is a proxy risk factor leading to ADHD by independent mechanisms. Smoking during pregnancy is associated with poorer parenting skills, which are associated with child behavioral problems.[43]

The current study has several strengths, including being based on a large nationwide sample, assessing nicotine exposure with objective biological measurement and including several potential confounders. However, when interpreting the findings, several limitations should be considered. A key question is whether smoking during pregnancy is causally associated with ADHD or is a proxy of another risk factor (eg, familial confounding). Even if most of the effect is due to familial or genetic confounding, the current study reveals that the association between smoking and ADHD has a dose-response effect. The limitation of observational data is that we cannot examine causal processes. We did not have access to biomarkers of sibling pregnancies that would have shed more light on a possible causal link between nicotine exposure during pregnancy and offspring ADHD. However, in the current study, we were able to adjust for several confounders, including BWGA, maternal SES, age, psychopathology, and substance use disorder as well as paternal psychopathology. Information about possible substance use during pregnancy was restricted to register-based substance use diagnoses. In the current study, 5.3% of mothers of children with ADHD had a diagnosis of substance use disorder, which was similar to the estimated prevalence in Finland of 6.4% for the exposure to maternal alcohol and drug dependence.[44] The number of parents diagnosed with ADHD in this sample was low, which is a limitation of the study (Supplemental Tables 5 and 6). The underdiagnoses among parents could be primarily because ADHD was not a widely used diagnosis in the parental generation. In addition, it is unlikely that ADHD among parents was treated in inpatient care. Because the FHDR did not cover outpatient diagnoses before 1998, the diagnosis of ADHD among parents is likely underestimated. Finally, the subjects with ADHD included in this study were only those who were referred to specialized services and likely represent the more severe cases of ADHD. However, authors of a previous study reported an 88% validity of the ADHD diagnoses in the FHDR examined against Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria for ADHD.[7]

CONCLUSIONS

According to the World Health Organization, smoking is considered 1 of the main public health concerns worldwide.[45] The current study reveals a strong association between prenatal nicotine exposure and a dose-dependent relationship with offspring ADHD. This study adds 2 important aspects; first, the use of cotinine as a documented measure of nicotine exposure during pregnancy and second, the finding of a dose-response effect in the association. Given the high prevalence of both smoking during pregnancy and ADHD among children, these findings warrant future studies on the interplay between maternal smoking and environmental, genetic, and epigenetic factors.

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ABBREVIATIONS

ADHD: attention-deficit/hyperactivity disorder
BWGA: birth weight for gestational age
CI: confidence interval
FHDR: Finnish Hospital Discharge Register
FMBR: Finnish Medical Birth Register
FMC: Finnish Maternity Cohort
ICD-8: International Classification of Diseases, Eighth Revision
ICD-9: International Classification of Diseases, Ninth Revision
ICD-10: International Classification of Diseases, 10th Revision
OR: odds ratio
PIC: personal identity code
SES: socioeconomic status

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